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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,814	05/11/2005	Rainer Hipfel	P67564US1	4911

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JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

EXAMINER	
STANDLEY, STEVEN H	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,814	HIPFEL ET AL.	
	Examiner	Art Unit	
	STEVEN H. STANDLEY	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *11-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of claims 1-10 in the reply filed on 2/08/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 11-32 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/08/08.

Priority

2. Priority is to the provisional application 60/348,674 filed 1/17/02.

Information Disclosure Statement

3. The IDS submitted 5/11/05 has been considered by the examiner.

Sequence Compliance

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because 37 CFR 1.821 (a)(2)(c-d) states that each sequence disclosed must appear separately in the sequence

listing and in the text of the description and claims whenever described. For example, a SEQ ID NO: and sequence listing is required for the DNA sequences on pages 36-38 of the specification. See MPEP 2422 & 2431. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821-1.825).

Claim Objections

5. Claim 1 is objected to because of the following informalities: It contains a reference to 'SCN2A,' and without first disclosing the meaning of the acronyms in the claims. In order to make the description of the invention more clear, the first claim that mentions these acronyms should fully express the phrase, and be followed by parentheses, which identify the acronym to be used in the following claim(s). Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of measuring SCN2A levels in the brain, does not reasonably provide enablement for a method of diagnosing or prognosticating (foretelling) a generic neurodegenerative disease or determining whether a subject is at increased risk of a generic neurodegenerative disease or Alzheimer's disease (AD) with the full-length SCN2A transcript, protein, a fragment, derivative or variant thereof. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:
1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The invention is complex because it diagnoses, prognosticates, and assesses the risk (all at the same time) of any generic neurodegenerative disease (of which there are many unrelated ones) by measuring a fragment of the transcription or translation product (which can be 2 base-pairs or amino acids; a length at which thousands of other genes share that same sequence). Thus, it accomplishes foretelling, diagnosing, and risk-assessing of an enormously complex and unrelated array of diseases by measuring fragments that are undoubtedly shared by thousands of complex and unrelated genes. The invention is also complex because it diagnoses, foretells, and assesses the risk of Alzheimer's disease, an inflammatory degenerative disease with no known relationship to SCN2A.

The prior art indicates the lack of expression of SCN2A in mice results in perinatal death by ischemia and neuronal cell death (Planelles-Cases et al.; see abstract; Applicant's IDS), and that mutation of the S4-S5 cytoplasmic linker in SCN2A results in a gain-of-function mutation causing seizure and behavioral abnormalities (see Kearney et al.; Applicant's IDS). However, these diseases

have no relationship to Alzheimer's disease nor any other neurodegenerative disease, and the art is silent even to this day on SCN2A being related to AD, prognostic of AD, or diagnostic of AD.

The working examples show an elevation in SCN2A mRNA as measured by PCR fragments generated from the mRNA in postmortem tissue from already diagnosed AD patients versus controls. The working examples do not show that the increase in expression of SCN2A precedes the onset of AD symptoms, or symptoms of any other neurodegenerative disease. Therefor there is zero support for the expression level of SCN2A being prognostic of AD or any disease except the one taught by Planells-Cases et al. Moreover the specification does not demonstrate that any fragment, derivative, or variant of the gene is elevated above control. Further, the specification provides no relationship between SCN2A expression and the risk of AD. Finally, the specification provides no data or guidance as to whether SCN2A would be elevated in early stages of AD. Therefore it is entirely unclear as to whether it is even diagnostic.

Thus, given the complexity of the invention, the lack of support in the art, and the lack of teaching or guidance in the specification, one of skill in the art could not use the invention commensurate with the scope of the claims.

7. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification lacks written description of what constitutes measuring a fragment or variant or derivative of SCN2A to diagnose a neurodegenerative disease. The specification does not demonstrate that any fragment, variant, or derivative of SCN2A can be used as a prognostic, or a diagnostic. What is reduced to practice is a unique mRNA fragment of 74 b.p. of SCN2A that is elevated in postmortem AD patients (see pages 34-40 in the specification).

The specification also discloses one full-length cDNA sequence, but no derivatives or variants of the sequence are known or disclosed, nor disclosed as being elevated in AD versus control. The specification does not disclose what fragments of SCN2A or variants or derivatives can and cannot be used to measure a difference between AD patients and controls. It discloses measuring one fragment of 74 bp of AD versus control. Also, Applicant has disclosed no measurement of the polypeptide of SCN2A or fragment or variant thereof. Thus, not a single polypeptide fragment, variant or derivative is reduced to practice.

The level of predictability that fragments, variants and derivatives of the SCN2A mRNA or polypeptide will be elevated above control in AD versus control patients is very low, since thousands of proteins share similar sequences of both short mRNA fragments and short polypeptide fragments. Therefore the likelihood that any fragment will be diagnostic is very low and entirely unpredictable.

The level of skill in the art is not such that one could determine which fragments, variants or derivatives will or will not be elevated in AD versus control.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of the method of measuring both mRNA fragments and polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers* v. *Revel*, 25 USPQ2d 1601 at 1606 (CMC 1993) and *Amgen Inc.* v. *Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 5-6 rejected under 35 U.S.C. 102(b) as being anticipated by Planells-Cases et al. (2000; see IDS).

Planells-Cases et al. disclose a method of diagnosing a disease that results in massive apoptosis (see abstract) and thus is a neurodegenerative disease. Planells-Cases measure the mRNA from an SCNA2 gene that has been disrupted. See Figure 2A on page 2882 wherein mRNA from the gene is measured and compared to a control not suffering from a neurodegenerative disease is measured. A massive decrease in mRNA is diagnostic and predictive of the perinatal neurodegenerative disease to follow. Thus, the limitations of claims 1, and 5-6 are met.

9. Claims 1, and 4-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Nostrand et al. (US patent number 5, 427,931, issued in 1995).

Van Nostrand et al. disclose a method of diagnosing or prognosticating a neurodegenerative disease in a subject by measuring a protein that contains a fragment of the translation product of SCN2A. Van Nostrand measure amyloid abeta app in the diagnosis of AD. The protein shares a common tripeptide -LAA- (amino acids 10-12 in beta app; first page of patent) with the human SCNA2 sequence (amino acids 22-24). Thus, Van Nostrand et al meet the limitations of claim 1 and 4. Van Nostrand also use a controls subject not suffering from AD

(figure 7a-d). Van Nostrand et al. also clearly prognosticate AD in a patient (see example 27). Van Nostrand also measure APP in the blood and platelets which is a fluid and cell sample, which meets the limitations of claims 5-7.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 2-3, 8-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Planells-Cases et al. (2000).

Planells-Cases et al. teach the method as above. In short, they teach a neurodegenerative disease that follows from the disruption of the SCN2A gene which results in perinatal death due to ischemia and apoptosis.

Panells-Cases et al. do not explicitly teach a method of monitoring the progression of 'a neurodegenerative disease' in a subject. Further, they do not teach a method of evaluating a treatment as recited in claim 3, nor the taking of a series of samples for measurement as recited in claim 8, nor wherein the subject receives a treatment prior to one or more of said sample gatherings of claim 9, nor wherein the level of activity is determined before and after treatment in a patient as recited in claim 10.

However, one of ordinary skill in the art would have known from Planells-Cases that monitoring the mRNA level of SCN2A in a patient with little to no expression of SCN2A mRNA would be an effective means of determining if the disease related to the lack of SCN2A expression was getting better or worse. There would be a reasonable expectation of success because Planells-Cases show that the lack of expression of SCN2A results in massive apoptosis, whereas normal expression results in survival. One of ordinary skill in the art would have also known to use the measuring of SCN2A mRNA as a means of evaluating treatment for the same reasons described above. Moreover, one of ordinary skill would take a series of samples over time in an individual being monitored, and to take samples and test before and after treatment. Again, there would be a reasonable expectation of success because Planells-Cases

demonstrate the consequences of the expression and the lack of expression of the gene encoding SCN2A.

One of ordinary skill in the art would be motivated to do the above because Planells-Cases et al. clearly demonstrate the consequences of the expression of the gene and consequences of lack of expression. Thus one would be motivated to assess, diagnose, and prognosticate the disease by measuring the mRNA.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven Standley whose telephone number is **(571) 272-3432**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Stucker can be reached on **(571) 272-0911**.

The fax number for the organization where this application or proceeding is assigned is **(571) 273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Steve Standley, Ph.D.
5/15/08

/David S Romeo/
Primary Examiner, Art Unit 1647